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ORIGINAL ARTICLE

Microwave-assisted synthesis of α-aryl malonates: Key intermediates for the preparation of azaheterocycles

Mohamed A. Ibrahim *

Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA
Department of Organic Chemistry, College of Pharmacy, Misr University for Science and Technology, 6th of the October, P.O. Box: 77, Egypt
Department of Pharmaceutical Chemistry, Almaarefa Colleges for Science and Technology, Riyadh 11597, Saudi Arabia

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Diethyl malonate

Abstract We disclose a new microwave-assisted protocol for the effective α-arylation of diethyl malonate. The coupling of aryl halides with diethyl malonate proceeds smoothly in short reaction time in the presence of a catalytic amount of $Cu(OTf)_2$, 2-picolinic acid and Cs_2CO_3 in toluene using microwave irradiation. The resulting α-aryl malonates are then used as key intermediates for synthesis of variety of heterocyclic compounds, including benzodiazepines, isoquinolines and pyrrolopyridine scaffolds.

1. Introduction

α-Aryl malonates represent an important class of molecules that have various pharmaceutical applications. α-Aryl malonates have been used as effective modulators in mammalian cell membranes and as enzyme inhibitors (Gorssman and Varner, 1997). Malonate chemistry is the best way to synthesize highly functionalized compounds containing quaternary centers. (Canet et al., 1992; Martin, 1980) α-Aryl malonates are used to synthesize a wide range of valuable intermediates in organic chemistry. One of these important intermediates leads to synthesis of α-aryl carboxylic acids (Toone and Jones, 1991; Shunsaku et al., 1996; Narisano and Riva, 1999; Guanti et al., 1998; Chenevert and Desjardins, 1994; Knabe et al., 1987; Meester et al., 1986).

α-Aryl acids represent an important class of molecules that are found in numerous natural products, as well as find various pharmaceutical applications (Sheldrick et al., 1978; Kong and Andersen, 1993; Hedge et al., 1998). α-Aryl acids are used for synthesis of different nonsteroidal anti-inflammatory drugs. For example, α-Aryl acetic acids and α-aryl propionic acids are used for synthesis of indomethacin, sulindac, ibufenac & diclofenac and ibuprofen, naproxen & ketoprofen, respectively (Rieu et al., 1986).

Several methods for the synthesis of α-aryl acids have been reported in literature; these include palladium-catalyzed cross coupling of enolates with aryl halides (Culkin and Hatrwig, 2003; Aramendia et al., 2002; Djakovitch and Kohler, 2000), as well as Cu(I)-catalyzed arylation of diethyl malonate in the presence of proline (Xie et al.,

* Address: Department of Pharmaceutical Chemistry, Almaarefa Colleges for Science and Technology, Riyadh 11597, Saudi Arabia. Tel.: +966531071097.
E-mail address: drmmonem@yahoo.com.
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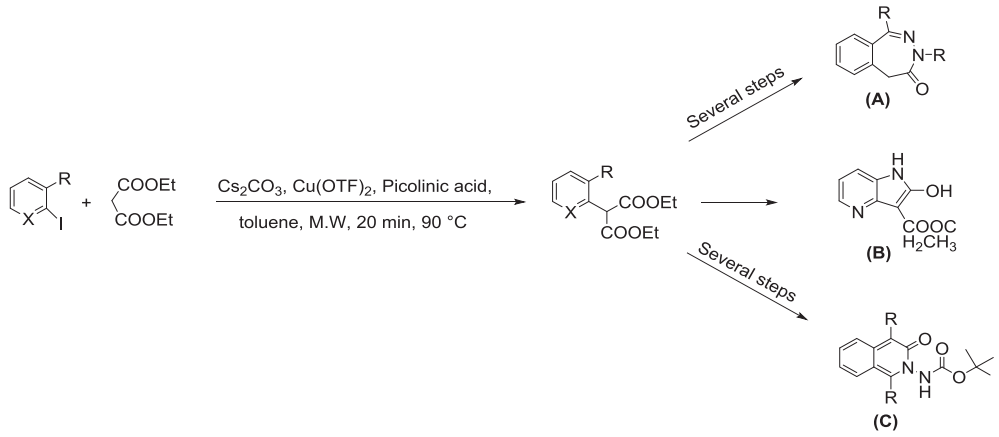
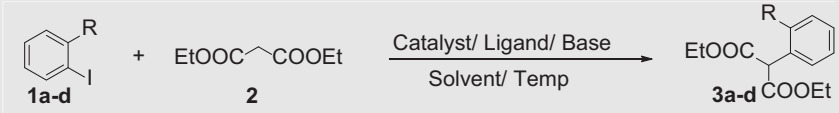


Scheme 1 Synthesis of substituted 2,3-benzodiazepine (A), substituted pyrrolopyridine ester (B) and substituted isoquinoline (C) scaffolds.

Table 1 Reagents and conditions for the arylation of diethyl malonate (DEM) with substituted iodobenzene.



R; **a**=$COOCH_3$; **b**=benzoyl; **c**= 4-methoxy benzoyl; **d**=nitrile

Entry	Catalyst	Ligand	Solvent	Temp. before adding DEM	Temp (°C)	Time (h)				Yield (%)[a]			
						1a	**1b**	**1c**	**1d**	**3a**	**3b**	**3c**	**3d**
1	No catalyst	No ligand	Dioxane	r.t.	r.t.	3	7	7	6	No reaction			
2	No catalyst	No ligand	Dioxane	90	90	3	7	7	6	No reaction			
3	CuI	Picolinic acid	Dioxane	r.t.	r.t.	3	14	14	6	6	5	8	8
4	CuI	Picolinic acid	Dioxane	90	90	3	7	7	6	71	63	80	84
5	CuI	Picolinic acid	Dioxane	r.t.	90	3	7	7	6	76	69	89	86
6	CuI	No ligand	Dioxane	90	90	3	7	7	6	14	12	11	14
7	CuI	No ligand	DCE	r.t.	90	3	7	7	6	No reaction			
8	CuI	No ligand	DMF	r.t.	90	3	7	7	6	No reaction			
9	CuI	Picolinic acid	Toluene	r.t.	90	3	7	7	6	78	69	90	89
10	Cu powder	Picolinic acid	Dioxane	r.t.	90	3	7	7	6	77	70	90	90
11	Cu powder	Picolinic acid	Toluene	r.t.	90	3	7	7	6	80	72	90	91
12	$AuCl_3$	Picolinic acid	Dioxane	r.t.	90	3	7	7	6	5	4	6	5
13	$Ag(CF_3CO_2)$	Picolinic acid	Dioxane	r.t.	90	3	7	7	6	No reaction			
14	$Cu(OTf)_2$	Picolinic acid	Dioxane	r.t.	90	3	5	5	6	83	75	91	94
15	$Cu(OTf)_2$	Picolinic acid	Toluene	r.t.	90	3	5	5	6	85	76	91	94
16	$Cu(OTf)_2$	Picolinic acid	Toluene	r.t.	M.W 90	0.5	0.5	0.5	0.5	86	75	91	95

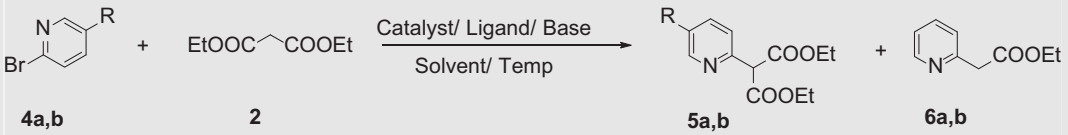
[a] Isolated yield.

2005; Buchwald, 2005). Nonetheless, several protocols may suffer serious limitations such as long reaction times, use of expensive metal catalysts, and low reactivity of pyridyl halides or halobenzonitriles toward palladium catalysts (Jiang et al., 2005; Fox et al., 2000; Culkin and Hartwig, 2001; Katz and Aube, 2003; Richon et al., 1982; Shiotani et al., 1996). Along with the lack of versatility in preparing such α-aryl malonates, the arylation of activated methylene compounds in the presence of copper metal or copper salts, known as Hurtley reaction, is only effective for *o*-bromobenzoic acid and its closely related halides (Hurtley, 1929). Reports on the Cu-mediated arylation of malonates and their derivatives by aryl halides indicate that often a stoichiometric amount of Cu complex is required; in addition, high reaction temperatures should be attained to allow the reaction to take place. Furthermore, good yields are only achieved in the case of highly activated aryl halides (Setsune et al., 1982; Suzuki et al., 1983, 1987). However, milder reaction conditions have been achieved as described by Buchwald, who reported the synthesis of a variety of arylated malonates from aryl iodides using CuI and 2-phenylphenol monodentate as a supporting ligand (Hennessy and Buchwald, 2002).

As a result of the importance of α-aryl malonates as intermediates for synthesis of a wide array of pharmaceutical agents, we developed an alternative general method that provides feasible access to a wide number of α-aryl malonates in short reaction time. Herein, we show the various optimization studied (bases, catalysts, ligands, solvents,

Table 2 Reagents and conditions for the arylation of diethyl malonate (DEM) with substituted bromopyridine.

bromopyridine.



4a,b **2** **5a,b** **6a,b**

R; **a**=H; **b**=Methyl

Entry	Catalyst	Ligand	Solvent	Temp. before adding DEM	Temp. (°C)	Time (h)	Yield (%)[a]	
							5a + **6a**	**5b** + **6b**
1	No catalyst	No ligand	Dioxane	r.t.	r.t.	14	No reaction	
2	No catalyst	No ligand	Dioxane	90	90	14	No reaction	
3	CuI	Picolinic acid	Dioxane	r.t.	r.t.	14	No reaction	
4	CuI	Picolinic acid	Dioxane	90	90	7: 14:	65% of **5a** 70% of **5a** + 15% of **6a**	35% of **5a** 39% of **5a** + 5% of **6a**
5	CuI	Picolinic acid	Dioxane	r.t.	90	7: 14:	85% of **5a** 80% of **5a** + 10% of **6a**	43% of **5a** 40% of **5a** + 6% of **6a**
6	CuI	No ligand	Dioxane	90	90	14	No reaction	
7	CuI	No ligand	DCE	r.t.	90	14	No reaction	
8	CuI	No ligand	DMF	r.t.	90	14	No reaction	
9	CuI	Picolinic acid	Toluene	r.t.	90	7: 14:	87% of **5a** 80% of **5a** + 10% of **6a**	45% of **5a** 41% of **5a** + 6% of **6a**
10	CuI	Picolinic acid	Toluene/$MgSO_4$	r.t.	90	7: 14:	88% of **5a** 81% of **5a** + 11% of **6a**	46% of **5a** 42% of **5a** + 6% of **6a**
11	Cu powder	Picolinic acid	Dioxane	r.t.	90	7: 14:	88% of **5a** 81% of **5a** + 11% of **6a**	47% of **5a** 42% of **5a** + 7% of **6a**
12	Cu powder	Picolinic acid	Toluene/$MgSO_4$	r.t.	90	7: 14:	88% of **5a** 81% of **5a** + 10% of **6a**	47% of **5a** 43% of **5a** + 7% of **6a**
13	$AuCl_3$	Picolinic acid	Dioxane	r.t.	90	14	No reaction	
14	$Ag(CF_3CO_2)$	Picolinic acid	Dioxane	r.t.	90	14	No reaction	
15	$Cu(OTf)_2$	Picolinic acid	Dioxane	r.t.	90	7: 14:	89% of **5a** 83% of **5a** + 11% of **6a**	52% of **5a** 47% of **5a** + 9% of **6a**
16	$Cu(OTf)_2$	Picolinic acid	Toluene/$MgSO_4$	r.t.	90	7: 14:	91% of **5a** 84% of **5a** + 12% of **6a**	54% of **5a** 49% of **5a** + 11% of **6a**

(*continued on next page*)

Table 2 (*continued*)

Entry	Catalyst	Ligand	Solvent	Temp. before adding DEM	Temp. (°C)	Time (h)	Yield (%)[a]	
							5a + **6a**	**5b** + **6b**
17	$Cu(OTf)_2$	Picolinic acid	Acetonitrile/$MgSO_4$	r.t.	90	7:	90% of **5a**	54% of **5a**
						14:	84% of **5a** + 12% of **6a**	49% of **5a** + 11% of **6a**
18	$Cu(OTf)_2$	Picolinic acid	Toluene/$MgSO_4$	r.t.	M.W 100	0.5:	91% of **5a**	55% of **5a**
						1:	84% of **5a** + 12% of **6a**	49% of **5a** + 12% of **6a**

[a] Isolated yield.

reaction times, reaction temperatures and leaving halides) toward the α-arylation of diethyl malonate. In addition, we employed the prepared α-aryl malonates for the synthesis of benzodiazepine, isoquinoline and pyrrolopyridine scaffolds.

2. Results and discussion

In a typical experiment, the desired aryl halides (1 mmole), cesium carbonate (3 mmole), copper triflate (0.1 mmole) and picolinic acid (0.2 mmole) were mixed together and flushed with argon. Anhydrous toluene was added followed by diethyl malonate (2 mmole). The mixture was irradiated in microwave at 90 °C for 30 min (Scheme 1).

Firstly, we investigated the α-arylation of diethyl malonate on substituted iodo benzene (methyl 2-iodobenzoate, 2-iodobenzophenone, 2-iodo 4-methoxybenzophenone and 2-iodobenzonitrile) (Table 1). In all cases, cesium carbonate was chosen as the base. In the absence of any catalyst/ligand, microwave irradiation resulted in no successful arylation (entries 1, 2). On the other hand, this reaction was sluggish at room temperature, even in the presence of various copper catalysts, picolinic acid as a ligand (entry 3). Indeed, heating at 90 °C in the presence of the aforementioned reagents resulted in better yields where diethyl malonate is later added to the reaction mixture (entries 4, 5). With respect to solvent effect, both 1,4-dioxane and toluene showed comparable efficiency (entries 5, 9, 10, 11, 14, 15). However, the presence of the ligand is critical given that low yield is obtained when no ligand was added in a solution of 1,4-dioxane while no reaction was observed when DCE or DMF was used (entries 6, 7, 8). When comparing the various metal catalysts, only copper salts (Cu powder, CuI and copper triflate) showed excellent convergent results (entries 5, 9, 10, 11, 14, 15), while auric chloride indicated little reaction progress and silver trifluoroacetate ($AgCF_3CO_2$) was entirely ineffective (entries 12, 13).

Finally, shorter reaction times were achieved when microwave oven was used in place of conventional heating methods. Indeed, optimum results can be obtained when Cs_2CO_3, copper triflate, and picolinic acid were used as additives in toluene at 90 °C for 30 min (entry 16).

Next, we aimed at investigating the scope of the arylation of diethyl malonate with N-heterocyclic compounds, namely, 2-bromopyridine and 2-bromo-5-methylpyridine (Table 2).

In all the following reaction trials, we used cesium carbonate as a base. The reaction resulted in no successful arylation in the presence of other bases (ALO-, $Ba(OH)_2$, NaH). The reaction did not work without any catalyst or ligand (entries 1, 2). Doing the reaction at room temperatures using copper salts as a catalyst, picolinic acid as a ligand and cesium carbonate as a base did not show a good progress (entry 3). The reaction did not work in the absence of picolinic acid in different solvents (dioxane, DCE, DMF) (entries 6–8).

α-Arylation of diethyl malonate on 2-bromopyridine **4a** for 7 h yielded **5a** in 65–91% yield while arylation of 2-bromo-5-methylpyridine **4b** for the same period afforded **5b** in 35–55% yield according to the employed conditions. On the other hand, longer reaction times using either **4a** or **4b** as a starting material (14 h) results in a mixture of **5a** and **6a**, and **5b** and **6b**, respectively (entry 5). Similarly, solvents with different polarity (dioxane, toluene, acetonitrile) were examined; toluene showed the best results especially upon addition of $MgSO_4$ as a drying agent (entries 10, 12, 16, 18). Acetonitrile exhibited almost

similar results as toluene (entry 17). Auric chloride and silver salt did not show any reaction progress (entries 13, 14).

Copper salts (Cu powder, CuI and copper triflate) in toluene/$MgSO_4$ showed the best results (entries 10, 12, 16). Microwave irradiation has been used to optimize the reaction conditions. The reaction proceeded in the presence of cesium carbonate, $Cu(OTf)_2$ and picolinic acid in toluene/$MgSO_4$ under microwave irradiations for 30 min to give **5a** in 91% yield (entry 18). Increasing the irradiation time to 1 h gives mixture of **5a** and **6a** in 84% and 12% yields respectively. (entry 18).

Next, we tested the arylation of diethyl malonate on 2-chloro-3-nitropyridine, 2-chloro-5-nitropyridine and 2,6-dichloro-3-nitropyridine (Table 3). In all the following reaction trials, we used cesium carbonate as a base. The reaction has been progressed at room temperature without ligand and catalyst due to presence of electron withdrawing group (nitro group) (entry 1). Heating the reaction at 90 °C gives almost the same results but with shorter reaction time (entry 2). Using picolinic acid ligand and the copper salt catalyst and stirring at room temperature for 2 h improves the yield (entries 3, 6, 8) while heating the previous mixture gives better yields than stirring at room temperature (entries 5, 7, 9). Different positions of the nitro group in either the *ortho* (**7a**) or the *para* (**7b**) positions did not show significant difference in the reaction yield (entry 10). The best reaction result has been obtained when we used microwave. The reaction proceeds well in the presence of cesium carbonate, copper triflate, and picolinic acid in toluene at 90 °C for 20 min (entry 10). Cesium carbonate worked at room temperature for only 60 min with high yield while other bases in the literature need high temperatures for long time (Shirude et al., 2013; Li, 2011; Dunn et al., 2009; Frank et al., 2013; Alam et al., 2013).

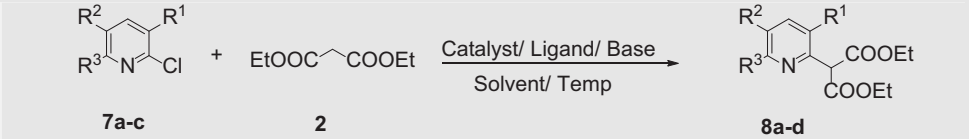
Different reaction conditions have been investigated for arylation of diethyl malonate on 2,6-dichloro-3-nitropyridine. When the reaction is performed at room temperature, it gives only one product (entries 1, 3, 6, 8). Heating the reaction mixture under different conditions gives mixture of the monoarylated product in high yield and the diarylated product in low yield (entries 5, 7, 9, 10).

After screening different reaction conditions on synthesis of α-aryl derivatives of diethyl malonate, we found that using catalytic amount of $Cu(OTf)_2$, 2-picolinic acid and Cs_2CO_3 in toluene using microwave irradiation is the ideal condition. Under these conditions, the reaction gives high yields in short reaction time.

The devised protocol overcomes some drawbacks in the literature including long reaction time, low yields, and poor reactivity of aryl bromide, and is applicable toward substrates containing certain functional groups in the *ortho* position (e.g., $–NO_2$, –CN) (Hennessy and Buchwald, 2002).

As our research interest involves the preparation and study of azaheterocycles (Elagawany et al., 2013; Ibrahim et al.,

Table 3 Reagents and conditions for the arylation of diethyl malonate (DEM) with substituted chloropyridine.



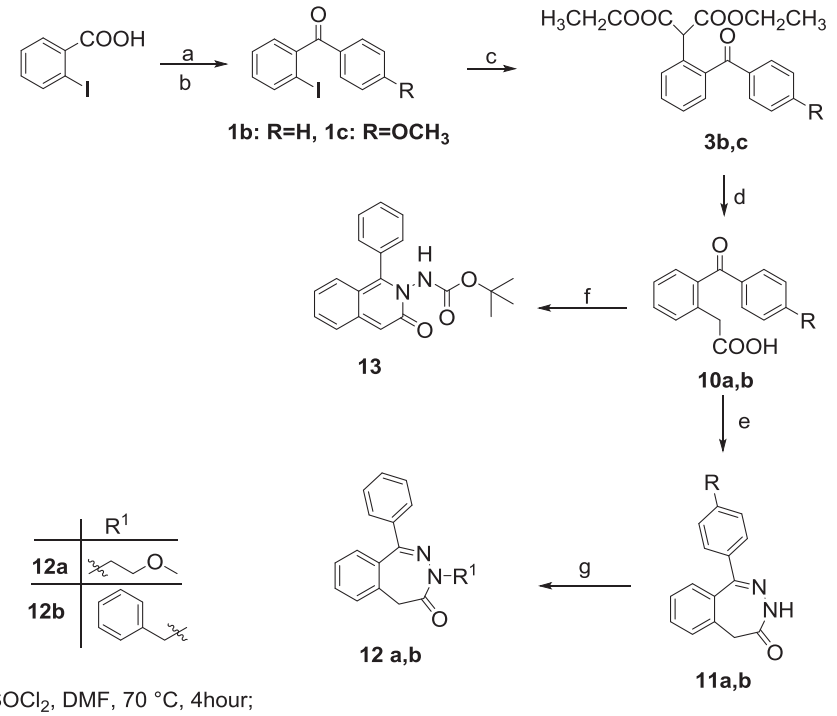
7a-c **2** **8a-d**

	R^1	R^2	R^3
7a	NO_2	H	H
7b	H	NO_2	H
7c	NO_2	H	Cl

	R^1	R^2	R^3
8a	NO_2	H	H
8b	H	NO_2	H
8c	NO_2	H	Cl
8d	NO_2	H	COOEt, COOEt

Entry	Catalyst	Ligand	Solvent	Temp. before adding DEM	Temp. (°C)	Time (h)			Yield (%)[a]		
						7a	**7b**	**7c**	**8a**	**8b**	**8c** + **8d**
1	No catalyst	No ligand	Toluene	r.t.	r.t.	2	2	2	70	69	60% **8c**
2	No catalyst	No ligand	Toluene	r.t.	90	1	1	1	73	70	65% **8c**
3	CuI	Picolinic acid	Toluene	r.t.	r.t.	2	2	2	75	72	68% **8c**
5	CuI	Picolinic acid	Toluene	r.t.	90	1	1	1	80	79	70% **8c** + 20% **8d**
6	Cu powder	Picolinic acid	Toluene	r.t.	r.t	2	2	2	76	72	69% **8c**
7	Cu powder	Picolinic acid	Toluene	r.t.	90	1	1	1	81	80	71% **8c** + 22% **8d**
8	$Cu(OTf)_2$	Picolinic acid	Toluene	r.t.	r.t.	2	2	2	85	85	75% **8c**
9	$Cu(OTf)_2$	Picolinic acid	Toluene	r.t.	90	1	1	1	88	90	75% **8c** + 21% **8d**
10	$Cu(OTf)_2$	Picolinic acid	Toluene	r.t.	M.W 90	0.2	0.2	0.2	87	90	75% **8c** + 22% **8d**

[a] Isolated yield.



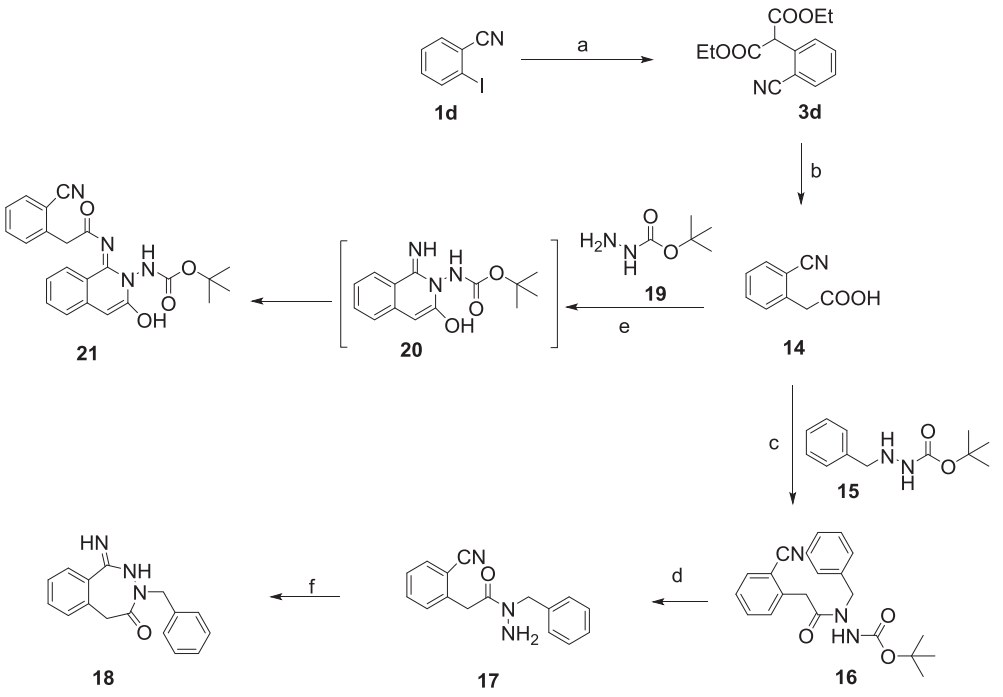
(a) $SOCl_2$, DMF, 70 °C, 4hour;
(b) $AlCl_3$, 70C, benzene (1a) or anisole (1b), 5hour;
(C) Cs_2CO_3, $Cu(OTF)_2$, Picolinic acid, toluene, M.W, 20 min, 90 °C;
(d) $LI(OH)_2$, 120 °C, H_2O/Methanol, 5 min, M.W.;
(e) Hydrazine hydrate, Isopropanol, M.W, 140 °C, 1hour;
(f) tert-butyl-carbazate, EDCI, $(Et)_3N$, r.t., 4hour;
(g) Chloro-2-methoxy ethane (12a) or benzyl chloride (12b), Cs_2CO_3, THF, M.W, 120 °C, 15minutes.

Scheme 2 Synthesis of benzodiazepine derivatives **12a**,**b** and isoquinoline scaffold **13**.

2013, 2012), we employed the prepared α-aryl malonate in the synthesis of benzodiazepine, isoquinoline and pyrrolopyridine scaffolds (Scheme 1).

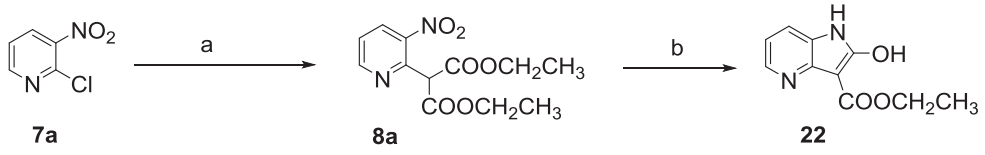
Firstly, the role of α-aryl malonate in the synthesis of 2,3-benzodiazepine-4-one and isoquinoline scaffolds has been described. Commercially available 2-iodobenzoic acid was activated into the corresponding aroyl chloride which is then involved in a Friedel–Crafts reaction in the presence of benzene to give **1b** or methoxybenzene to give **1c**. Then, we synthesized α-Aryl malonate derivatives **3b**,**c** by our optimized condition using diethyl malonate, copper-triflate and picolinic acid in toluene in microwave for 30 min. α-Aryl malonate derivatives were then decarboxylated in alkaline medium in microwave at 120 °C for 5 min in mixture of methanol and water to give the decarboxylated form **10a**,**b**. Condensation of the decarboxylated intermediate **10a**,**b** with hydrazine hydrate gives the corresponding 2,3-benzodiazepines-4-one **11a**,**b** while coupling the decarboxylated intermediate **10a** with tert-butyl-carbazate using EDCI, triethylamine and HOBt in dimethylformamide at room temperature for 7 h gives isoquinoline scaffold **13**. N-methylation of the amide function in compound **11a** was eventually performed with chloro-2-methoxy ethane and benzyl chloride in the presence of Cs_2CO_3 and tetrahydrofuran to give compounds **12a**,**b**. Our methodology for synthesis of 2,3 benzodiazepine derivatives is more time saving and gives higher yield (29% overall yield, 8.5 h) than literature method (14% overall yield, more than 3 days) (Mcdonald and Dunstone, 2006; Flammang and Wermuth, 1976) (Scheme 2).

Further, the importance of α-aryl malonate in the synthesis of 1-imino-2,3 benzodiazepine-4-one and substituted 1-imino-isoquinoline has been described. (Scheme 3) A copper-catalyzed reaction was performed on 2-iodobenzophenone leading to the substitution of the iodine atom by a diethyl malonate moiety using our optimized methodology in the presence of copper-triflate and picolinic acid in toluene in microwave for 30 min. Alkaline hydrolysis of α-aryl malonate **3d** in microwave at 120 °C for 5 min in mixture of methanol and water gives the decarboxylated form **14**. Coupling the decarboxylated intermediate with benzyl tert-butyl-carbazate **15** using BOP, triethylamine in dichloromethane at room temperature for 7 h gives compound **16** which is then deprotected by trifluoroacetic acid at room temperature for 10 min to compound **17**. Several trials were performed for intramolecular cyclization of the deprotected form **17** between the amino group and the nitrile group to obtain 1-imino-2,3 benzodiazepine-4-one **18**. The reaction has been investigated in trifluoroacetic acid at different temperature degrees starting from room temperature to 130 °C. Microwave irradiation of compound **17** in trifluoroacetic acid for 30 min at 135 °C gives compound **18** in 10% yield. Also, we tried to use isopropanol and butanol as solvents for intramolecular cyclization at 135 °C for 24 h but the yield was 5%. Coupling reaction of compound **14** with tert-butyl carbazate **19** in the presence of BOP and triethylamine at room temperature for 7 h gives the unseparated compound **20** which then attacks another molecule of compound **14** to give compound **21** in 83% (Scheme 3).



(A) Cs_2CO_3, $Cu(OTF)_2$, picolinic acid, toluene, M.W, 20 min, 90 °C.
(b) $Li(OH)_2$, 120 °C, H_2O/Methanol, 5 min, M.W.
(c) benzyl tert-butyl-carbazate, EDCI, $(Et)_3N$, r.t.
(d) CF_3COOH, r.t., 10 min.
(e) tert-butyl-carbazate, EDCI, $(Et)_3N$, r.t., 4hour.
(f) triflouroacetic acid/ M.W/ 120°C, 5 minutes.

Scheme 3 Synthesis of 1-imino 2,3 benzodiazepine **18** and 1-imino isoquinoline **21** scaffolds.



(a) Cs_2CO_3, $Cu(OTF)_2$, Picolinic acid, toluene, M.W, 20 min, 90°C;
(b) Fe, acetic acid, 120°C, 2hr or in microwave at 130°C,15 minutes.

Scheme 4 Synthesis of pyrrolopyridine ester **22**.

Furthermore, α-aryl malonate has been used in synthesis of pyrrolopyridine scaffold. Our optimized copper-catalyzed reaction was performed on the commercially available 2-chloro-3-nitropyridine to give **8a**. Cyclization of compound **8a** in acetic acid 100% and iron in microwave at 130 °C for 15 min gives pyrrolopyridine ester **22**. Our methodology for synthesis of pyrrolopyridine ester is more time saving and gives higher yield (82% overall yield, 35 min) than literature method (10% overall yield, 13 h) (Dogan et al., 2015) (Scheme 4).

3. Conclusion

In conclusion, an efficient and simple method to synthesize the α-aryl diethyl malonates in good yields and shorter reaction time is described. The optimized condition is achieved by using catalytic amounts of copper triflate, picolinic acid and Cs_2CO_3 in toluene using microwave irradiation. Then, α-aryl malonate was employed as intermediate for the synthesis of benzodiazepines, isoquinolines and pyrrolopyridine scaffolds. Currently, efforts toward the synthesis of new scaffolds using α-aryl malonates are underway.

4. Experimental

All materials from commercial suppliers were used as purchased. The melting points reported are uncorrected. ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 100 MHz. ^{1}H NMR spectra were recorded on a Bruker 300 MHz Avance DPX; probe dual. Chemical shifts are given in parts per million (ppm) relative to tetramethylsilane (TMS), and coupling constants *J* are given in Hertz. Mass spectra were determined by ESI–mass spectra obtained on an LC/MS instrument (AGILENT, MS:

MSD-SL, LC: 1200SL). For MW reactions, irradiation was performed using a Biotage Initiator EXP.

5. General procedure for α-arylation of diethyl malonate

The corresponding arylhalides **1a–d** or **4a**,**b** or **7a–c** (0.620 mmole), cesium carbonate (615 mg, 1.860 mmole), copper triflate (22 mg, 0.062 mmole), picolinic acid (15 mg, 0.124 mmole) were mixed together and flushed with argon. Anhydrous toluene (2 mL) was added followed by diethyl malonate (195 μL, 1.240 mmole). The mixture was irradiated by microwave at 90 °C for 30 min. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate and washed with ammonium chloride, saturated solution of sodium bicarbonate and brine solution. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography using gradient of ethyl acetate/heptane to give the corresponding arylated malonate **3a–d** or **5a**,**b** or **6a**,**b** or **8a–d** respectively.

Diethyl 2-(2-(methoxycarbonyl)phenyl)malonate (3a): (Setsune et al., 1981) Starting reactant (**1a**). Oily (86%); Purification eluent; ethyl acetate/heptane 15%. ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 6H), 1.74 (s, 3H), 4.15–4.29 (m, 4H), 5.10 (s, 1H), 7.41–7.46 (m, 1H), 7.59–7.71 (m, 3H).

Diethyl 2-(2-benzoylphenyl)malonate (3b): (Kobayashi et al., 1994) Starting reactant (**1b**). Oily (75%); Purification eluent; ethyl acetate/heptane 15%. ^{1}H NMR ($CDCl_3$) δ 1.62 (t, J = 7 Hz, 6H), 4.09–4.18 (m, 4H), 5.05 (s, 1H), 7.33–7.42 (m, 4H), 7.47–7.60 (m, 3H), 7.73–7.76 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 14.0, 54.4, 61.8, 127.3, 128.4, 129.8, 130.2, 130.4, 131.0, 132.6, 133.3, 137.7, 138.4, 168.2, 197.5.

Diethyl 2-(2-(4-methoxybenzoyl)phenyl)malonate (3c): Starting reactant (**1c**). Oily (91%); Purification eluent; ethyl acetate/heptane 15%. ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz, 6H), 3.84 (s, 3H), 4,09–4,20 (m, 4H), 5.00 (s, 1H), 6.88–6.91 (m, 2H), 7.35–7.36 (m, 2H), 7.47–7.62 (m, 2H), 7.74–7.77 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 14.1, 55.7, 61.9, 113.8, 127.4, 129.3, 130.2, 130.5, 130.6, 132.3, 133.0, 139.1, 163.9, 168.4, 195.8.

Diethyl 2-(2-cyanophenyl)malonate (3d): (Beugelmans et al., 1982) Starting reactant (**1d**). Oily (95%); Purification eluent; ethyl acetate/heptane 20%. ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 6H), 4.10–4.25 (m, 4H), 5.05 (s, 1H), 7.36–7.41 (m, 1H), 7.54–7.66 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 14.2, 55.7, 62.5. 113.7, 117.3, 128.8, 130.1, 133.0, 133.1, 136.3, 166.9.

*5.1. Diethyl 2-(pyridin-2-yl)malonate (**5a**) + Ethyl 2-(pyridin-2-yl)acetate (**6a**)*

Using our generalized procedure gives mixture of **5a** + **6a**: Starting reactant (**4a**).

Diethyl 2-(pyridin-2-yl)malonate (5a): (Bob et al., 2009) Oily; Purification eluent; ethyl acetate/heptane 30%. ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 6H), 4.20–4.36 (m, 4H), 4.93 (s, 1H), 7.20–7.28 (m, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 8.55 (d, J = 4.3 Hz, 1H).

Ethyl 2-(pyridin-2-yl)acetate (6a): (Firth et al., 2014) Oily; Purification eluent; ethyl acetate/heptane 30%. ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 3.82 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 7.14–7.29 (m, 2H), 7.63 (t, J = 8.5 Hz, 1H), 8.54 (d, J = 4.3 Hz, 1H).

Diethyl 2-(5-methylpyridin-2-yl)malonate (5b) + Ethyl 2-(5-methylpyridin-2-yl)acetate (6b): (Beigelman et al., 2009; Akio, 2007) Using our generalized procedure gives mixture of **5b** + **6b**: Starting reactant (**4b**).

Diethyl 2-(5-methylpyridin-2-yl)malonate (5b): (Beigelman et al., 2009) Oily; Purification eluent; ethyl acetate/heptane 30%. ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 6H), 2.31 (s, 3H), 4.21–4.23 (m, 4H), 7.36 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8 Hz, 1H), 8.37 (d, J = 1.6 Hz, 1H).

Ethyl 2-(5-methylpyridin-2-yl)acetate (6b): (Akio, 2007) Oily; Purification eluent; ethyl acetate/heptane 30%. ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 2.29 (s, 3H), 3.78 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 7.16 (d, J = 8.0 Hz, 1H), 7.44 (dd, J = 7.8 Hz, 2 Hz, 1H), 8.36 (s, 1H).

Diethyl 2-(3-nitropyridin-2-yl)malonate (8a): (Shirude et al., 2013) Oily; Purification eluent; ethyl acetate/heptane 30%. ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 6H), 4.21–4.30 (m, 4H), 5.49 (s, 1H), 7.49–7.53 (m, 1H), 8.46 (d, 1H, J = 8.3 Hz, 1H), 8.77 (d, J = 4.7 Hz, 1H).

Diethyl 2-(5-nitropyridin-2-yl)malonate (8b): (Frank et al., 2013) Oily; Purification eluent; ethyl acetate/heptane 30%. ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6H), 4.21–4.29 (m, 4H), 5.04 (s, 1H), 7.74 (d, 1H, J = 8.6 Hz), 8.48 (dd, J = 8.7 Hz, 2.7 Hz, 1H), 9.36 (d, J = 2.5 Hz, 1H).

*5.2. Diethyl 2-(6-chloro-3-nitropyridin-2-yl)malonate (**8c**) + Tetraethyl 2,2′-(3-nitropyridine-2,6-diyl)dimalonate (**8d**)*

Our generalized procedure gives mixture of **8c** + **8d**: Starting reactant (**7c**).

Diethyl 2-(6-chloro-3-nitropyridin-2-yl)malonate (8c): (Alam et al., 2013) Oily; Purification eluent; ethyl acetate/heptane 30%. ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 6H), 4.10–4.14 (m, 4H), 5.39 (s, 1H), 7.74 (d, 1H, J = 8.6 Hz), 8.39 (d, 1H, J = 8.6 Hz).

Tetraethyl 2,2′-(3-nitropyridine-2,6-diyl)dimalonate (8d): Oily; Purification eluent; ethyl acetate/heptane 30%. ^{1}H NMR ($CDCl_3$) δ 1.21–1.27 (m, 12H), 4.16–4.30 (m, 8H), 4.94 (s, 1H), 5.46 (s, 1H), 7.74 (d, 1H, J = 8.6 Hz), 8.47 (d, 1H, J = 8.6 Hz). ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2, 59.6, 60.3, 62.3, 62.6, 124.6, 134.1, 148.5, 157.1, 166.3, 168.1, 168.4. Anal. calcd. for $C_{19}H_{24}N_2O_{10}$: C, 51.82; H, 5.49; N, 6.36; found: C, 51.83; H, 5.48; N, 6.35.

*5.3. General procedure for synthesis of compounds **10a**,**b***

A mixture of compounds **3b** or **3c** (0.58 mmole) and Lithium hydroxide (74.1 mg, 1.761 mmole) in methanol (2 mL) and water (1 mL) was irradiated in microwave at 120 °C for 5 min. The mixture was then diluted with saturated solution of Na_2CO_3 (20 mL) and extracted with ethyl acetate (20 mL). The aqueous layer was then acidified with conc. HCl to PH 2 and extracted by ethyl acetate (3 × 20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give compound **10a** or **10b**.

2-(3-Benzoylphenyl)acetic acid (10a): (Mcdonald and Dunstone, 2006) White microcrystal, m.p. = 105–107 °C (85%) ^{1}H NMR (CD_3OD) δ 3.86 (s, 2H), 7.34–7.53 (m, 6H), 7.58–7.63 (m, 1H), 7.75–7.77 (m, 2H). ^{13}C NMR (CD_3OD) δ 39.6, 127.7, 129.5, 131.1, 131.5, 132.2, 133.2, 134.3, 135.9, 139.2, 139.7, 174.9, 200.1.

2-(2-(4-Methoxybenzoyl)phenyl)acetic acid (10b): (Flammang and Wermuth, 1976; Tang et al., 2010; Dogan et al., 2015) White microcrystal, m.p. = 124–126 °C (80%) ^{1}H NMR (CD_3OD) δ 3.79 (s, 2H), 3.88 (s, 3H), 7.00 (d, J = 8.9 Hz, 2H), 7.37–7.42 (m, 3H), 7.48–7.52 (m, 1H), 7.77 (d, J = 8.9 Hz, 2H).

5.4. General procedure for synthesis of compounds **11a,b**

A mixture of **10a** or **10b** (1.23 mmole) and hydrazine hydrate (119.7 µL, 3.71 mmole) in isopropanol (2 mL) was irradiated in microwave for 1 h at 140 °C. The mixture was diluted in ethyl acetate and washed with saturated solution of sodium bicarbonate. The organic layer was purified by column chromatography using ethyl acetate/heptane 1:1 to give compound **11a** or **11b**.

1-Phenyl-2,3-benzodiazepin-4(3H)-one (11a): (Mcdonald and Dunstone, 2006; Flammang and Wermuth, 1976) White microcrystal, m.p. = 217–219 °C (65%) ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 2H), 7.23–7.63 (m, 9H), 9.20 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 42.3, 127.0, 128.2, 128.5, 129.4, 129.7, 130.1, 131.4, 132.0, 136.3, 136.0, 162.2, 171.3. m/z: 237 (m + 1).

1-(4-Methoxyphenyl)-2,3-benzodiazepin-4(3H)-one (11b): White microcrystal, m.p. = 232–234 °C (70%) ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 2H), 3.79 (s, 3H), 6.86 (d, J = 8.9 Hz, 2H), 7.17–7.19 (m, 1H), 7.24–7.32 (m, 2H), 7.43–7.50 (m, 3H), 8.64 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 42.3, 55.6, 114.0, 127.0, 128.2, 129.9, 130.5, 131.0, 131.5, 132.0, 136.4, 161.4, 162.2, 171.5. m/z: 267 (m + 1). Anal. calcd. for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52; found: C, 72.25; H, 5.64; N, 10.90.

5.5. General procedure for synthesis of compounds **12a,b**

A mixture of compound **11a** (100 mg, 0.424 mmole), cesium carbonate (152 mg, 0.466 mmole) in tetrahydrofuran (1 mL) and chloro-2-methoxy ethane (31 µL, 0.466 mmole) or benzyl chloride (56 µL, 0.466 mmole) was irradiated in microwave at 120 °C for 45 min. The solvent was evaporated and the residue was purified by flash chromatography using ethyl acetate/heptane 50% to give compound **12a** or **12b**. The reaction could be performed also using sodium hydride (11 mg, 0.466 mmole) in dimethylformamide (1 mL).

3-(2-Methoxyethyl)-1-phenyl-2,3-benzodiazepin-4-one (12a): oily (85%) ^{1}H NMR ($CDCl_3$) δ 3.29 (s, 3H), 3.46–3.66 (m, 4H), 4.11 (br s, 2H), 7.24–7.28 (m, 1H), 7.32–7.37 (m, 1H), 7.42–7.49 (m, 4H), 7.53–7.58 (m, 1H), 7.64–7.66 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 42.5, 49.5, 58.8, 69.9, 126.9, 127.9, 128.5, 129.4, 129.6, 130.3, 131.1, 132.1, 137.1, 138.1, 162.6, 167.9 m/z: 295 (m + 1). Anal. calcd. for $C_{18}H_{18}N_2O_2$: %C, 73.45; H, 6.16; N,9.52; found: 73.80; H, 6.22; N,9.19.

3-benzyl-1-phenyl-2,3-benzodiazepin -4-one (12b): oily (84%) ^{1}H NMR ($CDCl_3$) δ 3.39–3.63 (m, 2H), 4.79–5.23 (m, 2H), 7.07–7.17 (m, 5H), 7.19–7.37 (m, 7H), 7.41–7.48 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 42.5, 53.7, 126.9, 127.3, 127.9, 128.2, 128.5, 128.7, 129.5, 130.4, 131.1, 132.2, 137.1, 137.6, 138.0, 163.3, 167.8. m/z: 327 (m + 1). Anal. calcd. for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N,8.58; found: C, 80.95; H, 5.56; N, 8.60.

5.6. Tert-butyl (3-oxo-1-phenylisoquinolin-2(3H)-yl)carbamate (**13**)

Method A: A mixture of compound **10a** (467 mg, 1.94 mmole), N-methyl morpholine (433 mg, 4.270 mmole), and BOP (946 mg, 2.130 mmole) was dissolved in dichloromethane. The mixture was stirred for 10 min at room temperature then tert-butyl-carbazate (257 mg, 2.138 mmole) was added and the reaction was stirred at room temp for 4 h. The solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate and washed with 1 N HCl, saturated solution of Na_2CO_3 and saturated solution of sodium chloride. The organic layer was then dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to dryness. The residue was purified by column chromatography using ethyl acetate/heptane 1:1 to give yellow microcrystal **13** in 83% yield.

Method B: EDCI, HCl (315 mg, 2.333 mmol) and triethylamine (812 µL, 5.831 mmol) were added to a solution of tert-butyl-carbazate (257 mg, 2.138 mmol), **10a** (467 mg, 1.944 mmol) and HOBt (946 mg, 2.130 mmol) in dimethylformamide (25 mL) and stirred for 7 h at room temperature under nitrogen. The solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate and washed with 1 N HCl, saturated solution of Na_2CO_3 and saturated solution of sodium chloride. The organic layer was then dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography using ethyl acetate/heptane 1:1 to give compound **13** in 95% yield.

White microcrystal, m.p. = 181–183 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 6.77–6.84 (m, 2H), 7.02–7.05 (m, 1H), 7.23–7.35 (m, 3H), 7.47–7.56 (m, 3H), 8.16 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 28.0, 82.8, 109.4, 117.0, 122.6, 125.3, 128.1, 128.4, 129.5, 129.7, 130.1, 131.7, 131.9, 143.5, 153.5, 159.3. m/z: 337 (m + 1). Anal. calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33; found: C, 71.42; H, 5.98; N, 8.33.

5.7. 2-(2-cyanophenyl)acetic acid (**14**): (Tang et al., 2010)

A mixture of compound **3d** (442 mg, 1.692 mmole) and lithium hydroxide (227 mg, 5.412 mmole) in methanol (4 mL) and water (2 mL) was irradiated in microwave at 120 °C for 5 min. The reaction was diluted in water and saturated solution of $NaHCO_3$, and extracted with dichloromethane. The aqueous layer was acidified with Conc. HCl to PH 2, and extracted with dichloromethane; the organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure to give white microcrystal **14** in 81% yield, m.p.: 103–105 °C. ^{1}H NMR (CD_3OD) δ 3.87 (s, 2H), 7.42–7.50 (m, 2H), 7.60–7.73 (m, 2H). ^{13}C NMR (CD_3OD) δ 40.4, 114.6, 118.6, 129.0, 132.2, 133.9, 134.3, 140.0, 173.5.

Tert-butyl 2-benzyl-2-(2-(2-cyanophenyl)acetyl)hydrazinecarboxylate (16): A mixture of compound **14** (100 mg, 0.621 mmole), triethylamine (190 µL, 1.365 mmole) and BOP (302 mg, 0.683 mmole) in dichloromethane (2 mL) was stirred at room temperature for 3 min. Then, tert-butyl 2-benzylhydrazinecarboxylate (138 mg, 0.621 mmole) was added and the mixture was stirred at room temperature for 14 h. The mixture was diluted with DCM, washed with saturated solution of $NaHCO_3$, and purified by flash chromatography (ethyl acetate/heptanes 40%) to give oily compound **16** in 70% yield. ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 3.72–3.77 (m, 1H), 4.06–4.11 (m, 2H), 5.21–5.37 (m, 1H), 6.44 (s, 1H), 7.17–7.56 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 28.2, 38.1, 50.8, 82.6, 113.4, 118.0, 127.6, 128.2, 129.0, 129.2, 131.1, 132.7,

132.9, 135.2, 139.3, 154.1, 171.9. Anal. calcd. for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50; found: C, 69.01; H, 6.33; N, 11.51.

N-benzyl-2-(2-cyanophenyl)acetohydrazide (17): Compound **16** (50 mg, 0.136 mmole) was dissolved in trifluoroacetic acid (2 mL) for 5 min. Trifluoroacetic acid was evaporated; the residue was diluted in ethyl acetate, washed with saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered, evaporated, and purified by flash chromatography ethylacetate/heptanes 1:1 to give compound **17** in 90% yield. m.p.: 120–122 °C. ^{1}H NMR ($CDCl_3$) δ 3.68 (br s, 2H), 4.25 (br s, 2H), 4.77 (br s, 2H), 7.25–7.48 (m, 7H), 7.44–7.66 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 38.7, 53.4, 113.6, 118.3, 127.2, 128.2, 128.6, 128.7, 129.1, 130.7, 132.8, 135.4, 140.6, 172.0. Anal. calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84 found: C, 72.45; H, 5.71; N, 15.80.

3-benzyl-1-imino-1,2,3,5-tetrahydro-4H-benzo[d][1,2]diaze pin-4-one (18): Compound **17** (50 mg, 0.188 mmole) dissolved in trifluoroacetic acid (1 mL) was irradiated in microwave at 120 °C for 5 min. Trifluoroacetic acid was evaporated under reduce pressure and the residue was purified by flash chromatography ethylacetate/heptanes 1:1 to give compound **18** in 10% yield. ^{1}H NMR ($CDCl_3$) δ 3.08 (br s, 1H), 3.70 (br s, 2H), 4.62 (br s, 1H), 5.31 (br s, 2H), 7.23–7.29 (m, 3H), 7.32–7.42 (m, 3H), 7.48–7.74 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 39.0, 51.6, 127.4, 127.6, 128.5, 128.7, 129.1, 130.8, 132.6, 132.8, 136.3, 139.2, 162.2, 167.7. *m/z*: 266 (m + 1). Anal. calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84 found: C, 72.44; H, 5.69; N, 15.83.

*5.8. Tert-butyl (1-((2-(2-cyanophenyl)acetyl)imino)-3-hydroxyisoquinolin-2(1H)-yl)carbamate (**21**)*

A mixture of compound **19** (100 mg, 0.621 mmole), BOP (302 mg, 0.683 mmole), and triethylamine (190 µL, 1.365 mmole) in dichloromethane (4 mL) was stirred at room temperature for 3 min at room temperature then tert-butyl carbazate (82 mg, 0.621 mmole) was then added and the mixture was stirred at room temperature for 14 h. The reaction was diluted with dichloromethane and washed with saturated solution of Na_2CO_3. The organic layer was then dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to dryness. The residue was purified by flash chromatography ethyl acetate/heptanes 80% to obtain yellow microcrystal **21** in 75% yield. m.p = 183–185 °C.

^{1}H NMR (CD_3OD) δ 1.56 (s, 9H), 4.64 (s, 2H), 7.11–7.15 (m, 1H), 7.34–7.69 (m, 6H), 8.01 (d, J = 7.2 Hz, 1H), 8.99 (d, J = 8.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 28.8, 50.2, 81.9, 108.4, 114.1, 119.2, 121.8, 124.4, 126.5, 127.5, 131.8, 133.0, 133.4, 135.2, 141.2, 143.4, 155.7, 159.0, 159.3, 193.8. *m/z*: 417(m−1). Anal. calcd. for $C_{23}H_{22}N_4O_4$: C, 66.02; H, 5.30; N, 13.39; found: C, 66.00; H, 5.34; N, 13.35.

*5.9. Ethyl 2-hydroxy-1H-pyrrolo[3,2-b]pyridine-3-carboxylate (**22**): (Dogan et al., 2015)*

A mixture of compound **8a** (50 mg, 0177 mmole) and iron (29.7 mg, 0.537 mmole) in acetic acid 100% (1 mL) was irradiated in microwave at 130 °C for 15 min. Upon completion of the reaction, dichloromethane (25 mL) was added and iron is filtered on small piece of cotton. Dichloromethane was evaporated on rotavap to residue and purified by flash chromatography using gradient of 100% DCM to 10% MeOH/DCM to give scarlet red compound **22** in 95% yield.

^{1}H NMR (DMSO-d_6) δ 1.25 (t, J = 8.9 Hz, 3H), 4.21 (q, J = 7.0 Hz, 2H), 6.77 (t, J = 7.0 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 6.2 Hz, 1H), 10.3 (s, 1H), 12.5 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 14.8, 58.0, 82.6, 111.4, 111.5, 125.6, 131.1, 143.1, 164.1, 165.2. *m/z*: 207 (m + 1). Anal. calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59; found: C, 58.26; H, 4.91; N, 13.62.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2016.01.007.

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